TYPE 2 DIABETES
AN OVERVIEW OF THE SIGN GUIDELINE ON PHARMACOLOGICAL MANAGEMENT OF GLYCAEMIC CONTROL

GUIDANCE UPDATE

Production of this Guidelines supplement has been funded by an educational grant from Napp Pharmaceuticals Limited. The grant included an honorarium for the author. Napp Pharmaceuticals Limited has reviewed the supplement for technical accuracy and to ensure compliance with regulations. Napp Pharmaceuticals Limited has had no input into or editorial control of the content of this article, which resided with the author and Guidelines at all times. See page 8 for full disclaimer.

Date of preparation: March 2018

www.Guidelines.co.uk
A review of SIGN 154: Pharmacological management of glycaemic control in people with type 2 diabetes
Professor Gerard McKay, Consultant Physician, Department of Endocrinology, Diabetes and Clinical Pharmacology, Glasgow Royal Infirmary

Introduction
Historically, the management of hyperglycaemia in type 2 diabetes has been based on lowering glycated haemoglobin (HbA1c) as a surrogate marker, with only metformin and pioglitazone having cardiovascular outcome data. For metformin, this was based on a small sub study of the UK Prospective Diabetes Study (UKPDS), and, for pioglitazone, on the improvement in a secondary endpoint in the PROactive study. Following the finding of increased cardiovascular events with rosiglitazone, the regulatory authorities, initially in the USA in 2008 and then in Europe in 2012, mandated that all new treatments for the management of hyperglycaemia show no impact on cardiovascular morbidity and mortality. This has led to a number of large studies for newer drugs as part of their clinical development programme. For the most part no impact on cardiovascular morbidity and mortality, at least over the short term, has been shown, and there have been additional secondary benefits on weight loss and reduced incidence of hypoglycaemia. However, four drugs from two classes have now been shown to improve cardiovascular morbidity and mortality and three of these drugs, canagliflozin, empagliflozin, and lixivlitide are licensed for use in the UK.

The most recent NICE guidance (NICE Guideline 28 on Type 2 diabetes in adults: management) was first published in 2015 and does not capture the newest evidence. While SIGN 116 on The management of diabetes (2010) is considerably out of date. Given the likelihood of new evidence impacting on clinical practice, a rapid update of the chapter of SIGN 116 on pharmacological management of glycaemic control in people with type 2 diabetes was commissioned and published in late 2017 as a standalone guideline: Pharmacological management of glycaemic control in people with type 2 diabetes (SIGN 154).

Methodology
The guideline was developed using an adapted version of the standard SIGN guideline development process. Apart from including one meta-analysis that pooled randomised controlled trials (RCTs) already included in the original guideline, section 3 on targets for glycaemic control, was not updated. The rapid review approach for updating the guideline involved appraisal of five sources of evidence: the existing guideline, published as a chapter of SIGN 116; a series of systematic reviews developed by the Agency of Healthcare Research and Quality (AHRQ); NICE Guideline 28; a primary literature search to update these sources up to November 2016; cardiovascular outcome trials published during the development period of the guideline (up to September 2017).

A consultation period was held to further validate the finalised guideline as an evidence-based approach to help practitioners manage glycaemic control in people with type 2 diabetes; this included the publication of an algorithm to guide choice of first, second, and third-line agents (Figure 1).

Metformin
When compared with placebo or other agents, metformin is an effective blood glucose-lowering therapy. An AHRQ analysis showed that, when used as monotherapy, there was very little variation between the currently available classes of glucose-lowering medication. Adverse effects
Gastrointestinal side-effects are the most common adverse events associated with metformin therapy. The risk of hypoglycaemia is low, and weight gain is not a feature. The evidence shows that there is no risk of lactic acidosis specifically related to metformin use, but SIGN 154 advises using with caution in patients with moderate renal impairment.

Cardiovascular morbidity and mortality
There has been no new evidence relating to cardiovascular morbidity and mortality since UKPDS 34, which showed cardiovascular benefit of metformin in overweight patients with type 2 diabetes.

Metformin should be considered as the first-line oral treatment option for all people with type 2 diabetes.

Sulphonylureas
Sulphonylureas have been shown to be effective at lowering blood glucose levels. Evidence from trials comparing sulphonylureas with newer agents supports this, although these studies were designed to look at adverse effects, rather than directly comparing HbA1c reduction.

Adverse effects
Compared with newer agents, there are higher rates of hypoglycaemia and increased weight gain when using sulphonylureas. Sulphonylureas should be used with caution in patients with mild or moderate renal impairment and avoided in people with severe renal impairment.

Cardiovascular morbidity and mortality
There is no clear evidence to suggest that sulphonylureas are associated with increased cardiovascular morbidity and mortality.

Sulphonylureas should be considered as first-line treatment in people with type 2 diabetes who are intolerant of, or who have contraindications to, metformin, or as a second- or third-line add-on treatment. Caution should be used in those at risk of hypoglycaemia e.g. the elderly.

Thiazolidinediones
Pioglitazone is the only thiazolidinedione (TZD) with marketing authorisation in the UK, and evidence supports its use for lowering blood glucose.

Adverse effects
Pioglitazone is associated with weight gain, due, at least in part, to fluid retention, and there is also a risk of bladder cancer. As a class, TZDs are associated with an increased risk of fractures (in both men and women). There is no contraindication to using pioglitazone in renal impairment.

Cardiovascular morbidity and mortality
The PROactive study showed, as a secondary endpoint, improved cardiovascular outcomes with pioglitazone compared with placebo, but this is at the expense of an increased risk of heart failure. Pioglitazone should be considered for dual or triple therapy in the management of type 2 diabetes but should not be used in patients with heart failure. The risk of fracture should be considered with long-term use.

MANAGEMENT OF TYPE 2 DIABETES
### Management of Type 2 Diabetes

**First Line** in addition to lifestyle measures:

<table>
<thead>
<tr>
<th>SET GLYCAEMIC TARGET: HbA1c &lt;7% (53 mmol/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metformin</strong></td>
</tr>
</tbody>
</table>

**Usual Approach**

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>CV benefit</th>
<th>Hypoglycaemia risk</th>
<th>Weight</th>
<th>Main adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>Yes</td>
<td>Low</td>
<td>Reduction</td>
<td>Gastrointestinal</td>
</tr>
</tbody>
</table>

Second Line in addition to lifestyle measures:

<table>
<thead>
<tr>
<th>IF NOT REACHING TARGET AFTER 3–6 MONTHS, ADD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sulphonylurea</strong> or <strong>SGLT2 inhibitor</strong> or <strong>GLP-1 agonist</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>CV benefit</th>
<th>Hypoglycaemia risk</th>
<th>Weight</th>
<th>Main adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>No</td>
<td>High</td>
<td>Gain</td>
<td>Hypoglycaemia</td>
</tr>
</tbody>
</table>

Third Line in addition to lifestyle measures:

<table>
<thead>
<tr>
<th>IF NOT REACHING TARGET AFTER 3–6 MONTHS, REVIEW ADHERENCE:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Add either an additional oral agent from a different class</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Sulphonylurea</strong> or <strong>SGLT2 inhibitor</strong> or <strong>GLP-1 agonist</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 agonist*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>CV benefit</th>
<th>Hypoglycaemia risk</th>
<th>Weight</th>
<th>Main adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Yes (specific agents)*</td>
<td>Low</td>
<td>Loss</td>
<td>Gastrointestinal</td>
</tr>
</tbody>
</table>

Fourth Line in addition to lifestyle measures:

<table>
<thead>
<tr>
<th>IF NOT REACHING TARGET AFTER 3–6 MONTHS, REVIEW ADDITIONAL AGENT(S) FROM THIRD-LINE OPTIONS</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Basal insulin</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>CV benefit</th>
<th>Hypoglycaemia risk</th>
<th>Weight</th>
<th>Main adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Yes (specific agents)*</td>
<td>Low</td>
<td>Loss</td>
<td>Gastrointestinal</td>
</tr>
</tbody>
</table>

**Algorithm summarises evidence from the guideline in the context of the clinical experience of the Guideline Development Group. It does not apply in severe renal or hepatic insufficiency.**

Prescribers should refer to the British National Formulary (www.medicinescomplete.com), the Scottish Medicines Consortium (www.scottishmedicines.org.uk) and Medicines and Healthcare products Regulatory Agency (MHRA) warnings for updated guidance on licensed indications, full contraindications, and monitoring requirements.

* Continue medication at each stage if EITHER individualised target achieved OR HbA1c falls more than 0.5% (5.5 mmol/mol) in 3–6 months. Discontinue if evidence that ineffective.

---

**Figure 1: Algorithm for glucose lowering**

**Notes:**

- ONCE OSMOTIC SYMPTOMS RESOLVED, ADD **Sulphonylurea**, **SGLT2 inhibitor** or **Pioglitazone**.
- OR INDIVIDUALISED AS AGREED
- IF SEVERE OSMOTIC SYMPTOMS WITH WEIGHT LOSS OR POSSIBILITY OF TYPE 1 DIABETES (URGENT—PHONE SECONDARY CARE IMMEDIATELY).

---

**Table:**

<table>
<thead>
<tr>
<th><strong>OR INDIVIDUALISED AS AGREED</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALTERNATIVE APPROACH:</strong> if osmotic symptoms or intolerant of metformin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Sulphonylurea</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>CV benefit</th>
<th>Hypoglycaemia risk</th>
<th>Weight</th>
<th>Main adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>No</td>
<td>High</td>
<td>Gain</td>
<td>Hypoglycaemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>GLP-1 agonist</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>CV benefit</th>
<th>Hypoglycaemia risk</th>
<th>Weight</th>
<th>Main adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Yes (specific agents)*</td>
<td>Low</td>
<td>Loss</td>
<td>Gastrointestinal</td>
</tr>
</tbody>
</table>

**Review Adherence: Then Guided by Patient Profile**

1. **DPP-4 inhibitor** or **Pioglitazone**
   - **Basal Insulin**
     - High
     - Inject before bed
     - Use NPH (isophane) insulin or longer-acting analogues according to risk of hypoglycaemia;
     - Can reduce or stop sulphonylurea

2. **Sulphonylurea** or **SGLT2 inhibitor**
   - Can continue metformin, pioglitazone, DPP-4 inhibitor or SGLT2 inhibitor

3. **Add Prandial insulin or switch to twice-daily mixed biphasic insulin**

---

**Notes:**

- Consider dose reduction; Do not delay if first-line options not tolerated/inappropriate; *See full guideline pages 23 and 26–27; *See BNF: specific agents can be continued at reduced dose; *See BNF: no dose reduction required for linagliptin; *Pioglitazone is contraindicated in people with or with a history of heart failure or bladder cancer; Do not combine dapagliflozin with pioglitazone; *Caution with exenatide when eGFR<50 ml/min/1.73 m²; *Adjust according to response; *Driving, occupational hazards, risk of falls, previous history; HbA1c, – glycated haemoglobin; CV—cardiovascular; CKD—chronic kidney disease; CKD 3A—chronic kidney disease stage 3A (estimated glomerular filtration rate 45–59 ml/min/1.73 m²); SGLT2—sodium-glucose co-transporter-2; DPP-4—Dipeptidyl peptidase-4; BMI—body mass index.
DPP-4 inhibitors

Five dipeptidyl peptidase-4 (DPP-4) inhibitors are currently available in the UK, all have been shown to lower blood glucose, but the effect, at times, is modest.

Adverse effects

The evidence shows that DPP-4 inhibitors are associated with neither weight gain nor hypoglycaemia. Dose reduction for all DPP-4 inhibitors except linagliptin is required in renal impairment.

Cardiovascular morbidity and mortality

At the time of developing the guideline, three major cardiovascular outcome studies had been published for alogliptin (EXAMINE), saxagliptin (SAVOR-TIMI 53), and sitagliptin (TECOS), showing no increase in cardiovascular morbidity and mortality compared with placebo. Although the risk of lower limb amputation has not been seen in clinical trials for other agents in this class the European Medicines Agency has recommended that the product information of all SGLT2 inhibitors contains information on the risk of lower limb amputation.

There is some evidence that canagliflozin is beneficial in early diabetic nephropathy; it should be noted that SGLT2 inhibitors should not be initiated in individuals with chronic kidney disease and in the event of a decrease in estimated glomerular filtration rate, treatment should be adjusted depending on the individual agent.

Cardiovascular morbidity and mortality

There have been two large cardiovascular outcomes studies in this class: EMPA-REG and CANVAS for empagliflozin and canagliflozin, respectively. Both studies recruited patients with type 2 diabetes and a high risk of cardiovascular disease and those who were treated with an SGLT2 inhibitor had improved cardiovascular outcomes compared with placebo.

SGLT2 inhibitors should be considered as add on to metformin in people with type 2 diabetes.

In individuals with established cardiovascular disease SGLT2 inhibitors with proven cardiovascular benefit should be considered (empagliflozin or canagliflozin).

GLP-1 receptor agonists

There is evidence to support the efficacy of all glucagon-like peptide-1 (GLP-1) receptor agonists for lowering blood glucose, mainly as add on to oral therapy, but also in combination with insulin.

Adverse effects

The main side-effect resulting in discontinuation is gastrointestinal upset, GLP-1 receptor agonists are not associated with severe hypoglycaemia, unless used in combination with other blood glucose-lowering agents that are known to have this effect. Weight loss is a feature of this drug class. No dose adjustment is required in mild renal impairment, but advice for use and dose alteration in moderate and severe renal impairment varies between individual drugs.

Cardiovascular morbidity and mortality

In a study of patients with established cardiovascular disease, once-daily liraglutide showed improved outcomes compared with placebo, while both once-daily lixisenatide and once-weekly exenatide have demonstrated cardiovascular non-inferiority compared with placebo (placebo and standard of care).

Glucagon-like peptide-1 receptor agonist therapy should be considered in people with a body mass index \( \geq 30 \text{kg/m}^2 \) (or ethnicity-adjusted equivalent) in combination with oral agents or insulin as third- or fourth-line treatment. They are an alternative to insulin when oral agents are inadequate and, in those with established cardiovascular disease, GLP-1 receptor agonists with proven cardiovascular benefit, currently liraglutide, should be considered.

Insulin

All insulin preparations have efficacy in treating hyperglycaemia. When moving from oral to insulin therapy metformin should be continued but consideration should be given to discontinuing other glucose-lowering agents. Insulin is usually started as once-daily NPH insulin, but basal analogues can be considered if there are problems with recurrent hypoglycaemia or when an individual requires assistance with injections. Mixed insulin or prandial insulin are both valid options when intensifying treatment with the aim of optimising glycaemic control while minimising the risk of hypoglycaemia and weight gain.

Key points

- A rapid update of the chapter of SIGN 116 on pharmacological management of glycaemic control in people with type 2 diabetes was commissioned and published in late 2017 as a standalone guideline, SIGN 154
- The updated guideline considers the results of cardiovascular outcome trials published during the development period of the guideline
- Metformin should be considered as the first-line oral treatment option for all people with type 2 diabetes
- For individuals with established cardiovascular disease, evidence of proven cardiovascular benefit should be considered when choosing SGLT2 inhibitors or GLP-1 receptor agonists.

SGLT2=sodium glucose co-transporter 2; GLP-1=glucagon-like peptide-1

Conclusion

The updated guideline on the Pharmacological management of glycaemic control in people with type 2 diabetes (SIGN 154) was published in November 2017. The guideline is not intended to be overly prescriptive, but provides information to support the selection of appropriate treatment for individuals, guided by specific patient characteristics and needs.

Treatment choice should not exclude basic advice on the need for increased activity or dietary modification—the potential to deliver this as part of routine primary care was demonstrated in the recently published DIRECT study.

The updated guideline also prompts the prescriber to review treatment efficacy/safety at 3–6 months and to make changes, if necessary.

Underpinned by robust evidence and accompanied by an easy-to-follow treatment algorithm that can be used in the delivery of routine clinical care, the updated guideline should help improve the treatment of those with type 2 diabetes. Initial feedback on the guideline and its role in management has been positive.
Conflicts of interest

Professor McKay has received an honorarium from Napp Pharmaceuticals Limited for his work on this article and has been paid by many companies for advisory work and presentations relating to the management of type 2 diabetes. Professor McKay was a member of the guideline update group for SIGN 154.

References


Production of this supplement has been funded by an educational grant from Napp Pharmaceuticals Limited. The grant included an honorarium for the author. Napp Pharmaceuticals Limited has reviewed the supplement for technical accuracy and to ensure compliance with regulations. Napp Pharmaceuticals Limited has had no input into or editorial control of the content of this article, which resided with the author and Guidelines at all times.

The views and opinions in this supplement are not necessarily those of Napp Pharmaceuticals Limited or of Guidelines, its publisher, advisers, or advertisers.

Readers are strongly advised to refer to the summary of product characteristics when a guideline describes a drug therapy or when full details and the clinical significance of a product’s contraindications, special precautions, drug interactions, adverse reactions, or overdose are required. While every care has been taken to ensure the accuracy of this Guidelines supplement, this does not diminish the requirement to exercise clinical judgement and the publishers cannot accept liability for any errors and omissions.

The copyright of Guidelines (including the Guidelines brand, logo, and the design and format of the book) rests with MGP Ltd unless otherwise stated.

No part of this publication may be reproduced in any form without the permission of the publisher.

Date of preparation: March 2018

© MGP Ltd 2018